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(54) Title: METHOD AND DEVICE FOR LOADING A POROUS FRAMEWORK

(57) Abstract: The invention refers to a method and a device for loading a porous framework structure including a bicontinuous morphology in at least partial areas or having non- interconnected side-by-side pores with a fluid containing at least one bioactive component by using a pressure driven force for penetrating said fluid into said porous framework structure, said method comprises the following steps: - preparing or providing a three-dimensional body consisting at least partially of said porous framework structure having along one spatial direction two opposing frontal boundary surfaces, a first and second frontal boundary surface, being apart from each other and both of which adjoin at least one lateral boundary surface encircling said three-dimensional body, sealing air tightly said at least one lateral boundary surface, - adjoining air tightly a reservoir of said fluid at the first frontal boundary surface and - applying a pressure difference between the first frontal boundary surface and the second frontal boundary surface such that the fluid is penetrating through the porous framework structure along the spatial direction by pressure driven force only until the fluid exits over the entire second frontal boundary surface.



Method and device for loading a porous framework

Technical Field

The invention relates to a method and a device for loading a porous framework structure including a bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores with a fluid containing at least one bioactive component.

Background of the Invention

Porous framework structures which consists of biodegradable materials advantageously are used in the field of medicine as implants for example for bone building purpose, support or hold functions in intrakorporal tissue areas. Beside of the support or hold function of such porous framework structures which may have rigid, elastic or semielastic structural properties, the volume of the pores allows the inclusion of a medium containing bioactive components, like antibiotics and/or growth factors which can be delivered after implantation to a locally defined intrakorporal region of tissue. In such case the porous framework structure loaded with at least one bioactive component serves as a matrix-like reservoir which exerts it's intrakorporal therapeutic effect locally.

For loading the porous framework structure a plurality of loading techniques are known. The loading is very strong depending on the framework structure material as well on the material which is loaded into the porous framework structure.

In case of bioactive components all loading processes in which process temperatures occur above 100°C can be excluded because otherwise most antibiotics and growth

factors would be destroyed thermally. Wet chemical methods such as coupling fluids to the surface of the porous framework structure are due to the microporosity of the structure difficult to achieve and by the time required for sterilization of ceramics-antibiotics/growth factor complicated composites.

In addition to the pure loading of the porous framework structure and the associated storage of bioactive components, like drugs, the dynamic and temporal drug release from the matrix of the porous framework structure plays a very important role both in selecting materials and substances involved as well in regards of the loading technique. Concerning the dynamic and temporal drug release it is desired to reach release durations in periods of days, weeks or month.

For example when loading by means of adhesive processes such as dip and drip loading a longer term release is not guaranteed. Some studies show that an adhesive loading procedure is not suitable for longer term drug release, see for example Seidenstücker, M., et al., "Release kinetics and antibacterial efficacy of microporous β -TCP coatings", Journal of Nanomaterials, 2013, p. 8; or Bernstein, A., et al., "Microporous β -tricalciumphosphate (TCP) – a delivery vehicle of growth factors and drugs", Key engineering materials, 2013, 587, pages 93 to 96.

To enhance the time duration of drug delivery out of the implanted loaded porous framework structure the use of hydrogel as a carrier substance for the at least one bioactive component is more appropriate as an aqueous solution for loading purpose of the porous framework structure, since the hydrogel have a much higher viscosity compared to the aqueous solutions. Due to the much higher viscosity of hydrogels loading techniques like dip and drip loading or adhesive loading procedure are not applicable. Experimental procedures, such as loading with a centrifuge are also not practical, because a complete loading of the porous framework structure can't be ensured, see article of Itokazu, M., et al., "Development of porous apatite ceramic for local delivery of chemotherapeutic agents", J Biomed Mater Res, 1998, 39(4): p. 536 to 538.

Another approach for loading the porous framework network with a hydrogel containing bioactive components is mentioned in the article of Itokazu M., et al., "Synthesis of antibiotic-loaded interporous hydroxyapatite blocks by vacuum method and in vitro drug release testing", *Biomaterials*, 1998, 19(7-9), p. 817 to 819). The before mentioned article discloses a vacuum method, wherein the porous framework structure lying in the hydrogel is subjected to a vacuum by which the hydrogel enters the porous framework structure partially. The known vacuum method however does not lead to a complete filling of the whole pore volume, since the encapsulated air inside the porous framework structure escapes only partially, especially air contained near the core of the porous framework structure is subjected to an increase of volume only. As soon as normal pressure conditions are reached back the core area of the porous framework structure remains filled with air.

Summary of the Invention

It is an object of the present invention to provide a method as well a device for loading a porous framework structure including a bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores with a fluid containing at least one bioactive component such that the porous framework structure will be loaded completely, i.e. the whole pore volume shall be filled respectively loaded with the fluid containing the at least one bioactive component. Further it is desirable to use a fluid as the carrier of the at least one bioactive component which has the property that delivery of the bioactive component into the tissue environment after implantation occurs with a decelerated kinetics so that the time period in which drug delivery takes place can be extended up to several weeks or months starting with the event of implantation of the loaded porous framework structure. Further it is an object of the invention to realise the complete loading of the porous framework structure within a short time, i.e. less than one hour so that the condition is created to prepare a fluid with at least one bioactive agent individually adapted to patient and to load the

patient specific fluid into the porous framework structure during a surgical intervention performed on the patient. All means and process technologies that are required for the production of the loaded porous framework structure should be as easy to use and cost-effective manner.

The objects are achieved by the sum total of the features of the independent method claims 1. A device for a loading a three dimensional body made of a porous framework structure is disclosed inventively in the independent claim 14. The invention can be modified advantageously by the features disclosed in the sub claims as well in the following description especially referring to preferred embodiments.

The method for loading a porous framework structure including a bicontinuous morphology in at least partial areas or having non interconnected side-by-side pores with a fluid containing at least one bioactive component by using a pressure driven force for penetrating that fluid into that porous framework structure comprising the following steps inventively:

In a first step a three-dimensional body is prepared or provided consisting at least partially of said porous framework structure having along one spatial direction two opposing frontal boundary surfaces, a so called first and second frontal boundary surface, being a part from each other and both of which adjoin at least one lateral boundary surface encircling said three-dimensional body.

The term "bicontinuous morphology" describes a porous framework structure in which each pores are interconnected with each other.

The term "non-interconnected side-by-side pores" expresses an alternative structure design of pores which are formed in the form of non-interconnected and largely parallel to each other extending channels being directed along the before mentioned one spatial direction.

In a second step the at least one lateral boundary surface of the three-dimensional

body is sealed air tightly preferably by encapsulating said three-dimensional body with a silicon-encasement that is releasable fitted to the at least one lateral boundary surface of the three-dimensional body

In this state the three-dimensional body is on both sides, i.e. on the first and second frontal boundary surface, freely accessible.

In a next step a reservoir of said fluid containing the at least one bioactive component is connected to the first frontal boundary surface of the three-dimensional body so that the first frontal boundary surface adjoins air tightly the before mentioned fluid. In a last step a pressure different between the first frontal boundary surface adjoining air tightly to the reservoir and the second frontal boundary surface is applied such that the fluid penetrates through the porous framework structure along the spatial direction by pressure driven force only until the fluid exists over the entire second frontal boundary surface of the three-dimensional body.

In a preferred embodiment of the inventive method the pressure difference between the first and second frontal boundary surface is realized by applying an underpressure at the second frontal boundary surface and prevailing ambient pressure conditions in the fluid reservoir so that the fluid is sucked through the porous framework structure of the three-dimensional body caused by the vacuum pressure only. The step of vacuum pressurized fluid penetration through the porous framework structure takes place under room temperature conditions, i.e. at temperature between 15°C and 30°C. Under these temperature conditions no temperature caused degradation can take place at the at least one bioactive component within the fluid.

To ensure that the whole pore volume of the three-dimensional body can be filled with the fluid the first and second frontal boundary surfaces of the three-dimensional body should be of same size and shape preferably, in which the first and second frontal boundary surface overlap each other completely in projection of the spatial

direction. As soon as the fluid exists over the entire second boundary surface evidence is given that the whole pore volume is filled with the fluid, because it can be excluded that portions of the fluid can exist the three dimensional body elsewhere, for example at the at least one lateral boundary surface. It is also possible to use a three-dimensional body provided a second frontal boundary surface which is smaller or greater than the first frontal boundary surface for loading with the fluid inventively in which the second frontal boundary surface overlaps with the first frontal boundary surface completely or at least partially in projection of the spatial direction.

The three-dimensional body preferably has the shape of a wedge, a cube, a prism or a truncated cone but especially preferably in the shape of a straight cylinder. All the before mentioned three-dimensional geometries provide two frontal boundary surfaces facing each other along the one spatial direction. In case of a straight cylinder the first and second frontal boundary surfaces are of circular shape, in case of a wedge the first and second boundary surfaces are of triangle shape, in case of a cube the first and second frontal boundary surfaces are of square shape to name a view.

In all cases of appropriate forms of the three dimensional body the porous framework structure is made of a biodegradable ceramic material preferably and contains pores having mean pore diameter ranging between $1\mu\text{m}$ to $10\mu\text{m}$, preferably $2\mu\text{m}$ to $5\mu\text{m}$. The porous framework structure provides a porosity ranging between 30% and 50% preferably 40%. The first and second frontal boundary surface of the three-dimensional body are separates along the spatial direction by a distance ranging between 10 mm and 100 mm preferably between 20 and 50 mm.

As known from state of the art a preferred biodegradable ceramic material is a β -tricalciumphosphate (β -TCP) which is known for example from an article of Bernstein, A., et al., "Histological and histomorphometric investigations on bone integration of rapidly resorbable calcium phosphate ceramics", J Biomed Mater Res B Appl Biomater, 2008, 84(2), p. 452 to 462; or Mayr, H. O. et al., "Microporous pure beta-

tricalcium phosphate implants for press-fit fixation of anterior cruciate ligament grafts: strength and healing in a sheep model", Arthroscopy, 2009, 25(9), p. 996-1005.

For loading the porous framework structure with a fluid in a preferred embodiment a hydrogel is used which is an alginate sole in which the at least one bioactive component is an antibiotics and/or growth factors contained therein. Preferably the alginate sole bases on alginate mixed in distilled water. The dynamical viscosity η of the hydrogel ranges between 1,5 mPa·s and 10^5 mPa·s, preferably between 10^2 mPa·s and 2×10^4 mPa·s.

The pressure difference, which is applied between the first and second frontal boundary surface, for sucking the fluid respectively hydrogel through the porous framework structure of the three-dimensional body measures between 800 mbar and 1500 mbar, preferably $1000 \text{ mbar} \pm 100 \text{ mbar}$.

For the production of the pressure difference along the spatial direction through the porous framework structure of the three-dimensional body a vacuum source is connected to the second frontal boundary surface preferably, so that an under-pressure of about 50 mbar can be produced at the second frontal boundary surface, whereas in the fluid reservoir which is connected to the first frontal boundary surface of the three-dimensional body normal atmospheric pressure prevails. During the whole process of loading the porous framework network process temperatures does not exceed beyond room temperature significantly so that bioactive components like antibiotics or grove factors do not degrade or loose their bioactive properties.

The inventive method allows the production of an inventive three-dimensional body consisting at least partially of a porous framework structure which is of biodegradable material including said bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores in which the whole enclosed pore volume is filled completely with a fluid containing at least one bioactive component which has a heat resistance of less than 100°C preferably less than 70°C .

For an precise, simple and rapid manufacturing of the loaded three-dimensional body an inventively designed device is used which provides a casing into which said three-dimensional body is insertable such that a contact wall of said casing or a contact wall of an insert into the casing encloses the at least one lateral boundary surface of said three-dimensional body air tightly but loose. Further the casing provides along one spatial direction two opposing openings, a first and a second opening, in which the first opening is connected air tightly with a reservoir containing said fluid and said second opening is connected air tightly with a vacuum source.

In a preferred embodiment the contact wall of the casing or of the insert is made of flexible material, preferably made of silicon, which enables a smooth and air tight contact to the at least one lateral boundary surface of the three-dimensional body. As will be described in a further embodiment a preferred shape of the three-dimensional body is of straight cylindrical form which cylinder surface corresponds to the lateral boundary surface which is enclosed air-tightly by the contact wall of the before described casing or insert.

In a very simple embodiment the device for loading the three-dimensional body having the shape of a straight cylinder provides a hose which inner hose diameter corresponds to the diameter of the cylindrical three-dimensional body which is inserted into the hose so that the cylindrical surface matches the inner hose surface in a flush manner. At the one open hose end the reservoir filled with the fluid respectively hydrogel and at the other hose end a vacuum source are connected air tightly so that a directed pressure difference between both hose ends can be applied.

In the following a realized embodiment of loading a three-dimensional body made of a porous frame work structure is disclosed and described.

Brief Description of the Figures

The invention shall subsequently be explained in more detail based on exemplary embodiments in conjunction with the drawings. In the drawing

- Fig. 1 schematical images of a device for loading a three-dimensional body consisting of a porous frame work structure having a bicontinuous morphology or non-interconnected side-by-side pores,
- Fig. 2a-e longitudinal sections of three-dimensional bodies having different geometries,
- Fig. 3 illustration of a disassembled realized streaming chamber and
- Fig. 4 illustration of an assembled realized streaming chamber.

Detailed Description of exemplary Embodiments

Figure 1 shows a schematically longitudinal section view of a device for loading a three-dimensional body 1 consisting of a porous frame work structure having a bi-continual morphology, i.e. the pores of the frame work structure are interconnected to each other. The three-dimensional body 1 has the shape of a straight cylinder providing two circular end surfaces, namely a first frontal boundary surface 2 and a second surface boundary surface 3. In case of the straight cylindrical three-dimensional body 1 the two circular end surfaces 2, 3 adjoin a lateral boundary surface 4 which completely adjoin air tightly the inner wall 5 of a casing 6. Within the casing 6 the first and second frontal boundary surfaces 2, 3 of the three-dimensional body 1 are freely accessible.

For loading purposes the complete volume of the pores of the porous frame work

structure of the three-dimensional body 1 the casing 6 is connected to a reservoir 7 in which a fluid 8 is stored under ambient atmospheric pressure. Said fluid is an alginate sol hydrogel containing at least one bioactive component. To the opposite end of the casing 6 a vacuum source 9 is connected so that low pressure can be generated at the second frontal boundary surface 4 of the three-dimensional body 1, so that a pressure difference between the first frontal boundary surface 2 and the second frontal boundary surface 3 can be applied by which the fluid 8 will be sucked through the complete porous framework structure of the three-dimensional body 1. Hereby fluid enters the complete frontal boundary surface 2 and passes through the whole volume of the three-dimensional body so that the fluid 8 can exit over the complete second frontal boundary surface 3 to the left hand side of the casing 6 shown in fig. 1, see the arrows indicating the flow direction of the fluid 8 along the spatial direction through the porous body 1.

The three-dimensional body 1 advantageously consists of a micro-porous ceramic preferably a beta-tricalcium-phosphate (β -TCP) having a total porosity of around 40% interconnected micro pores that having an average pore diameter of 5 microns. The length of the cylindrical shape of the three-dimensional body can range between 10 mm and 100 mm, preferably between 20 mm and 50 mm. In a realized setting the length of the ceramic cylinder measures 26 mm and the cylinder diameter 7 mm. The fluid 8 provides preferably a dynamical viscosity η greater than said of water, i.e. the dynamical viscosity η ranges between 1,5 and 10^5 , preferably between 10^2 and 2×10^4 . In case of a realized embodiment the fluid 8 is a hydrogel, preferably an alginate sole, having self-curing properties. The hydrogel contains an antibiotics and/or growth factors additionally.

Alternatively the porous framework network of the three-dimensional body 1 can have a non-interconnected side-by-side pore structure which means that each of the pores are not-interconnected to each other but provides the nature of channels which completely penetrate the three-dimensional body and empty open at the first and second frontal boundary surface 2, 3.

In figures 2a to f longitudinal cross-sections of three-dimensional bodies are illustrated. In each case it is assumed that the direction of penetration of the fluid through the three-dimensional body 1 is from the right to the left which is indicated by the arrow. Figures 2a and b shows a three-dimensional body of truncated conical shape, figures 2c and d illustrates the longitudinal section of a wedge-shaped three-dimensional body, figure 2e shows a prismatic three-dimensional body and figure 2f a cubic shaped three-dimensional body. The list of illustrated examples is not limited so that other geometries are conceivable.

Figure 3 shows a realized device in a disassembled arrangement for loading a three-dimensional body (not shown), whereas figure 4 shows the device in an assembled state.

Figure 3 shows the device consisting of at least four separate components 10, 11, 12, 13 which can be assembled to a so called fluid type streaming chamber. The components 10 and 11 each provides a channel like recess 14 into which the three-dimensional body (not shown) can be inserted. The recesses 14 are coated with a flexible material, preferably made of silicon, which join the lateral boundary surface of the three-dimensional body, not shown in figure 3, air tightly. The components 10 and 11 can be fitted together by screws which are insertable into the holes 15 shown in figure 3.

Further components 12 and 13 each provides a connecting flank in which an O-ring 16 is integrated for a fluid and air tight connection with the flow chamber which results from the mated recesses 14 inside of the assembled components 10, 11. Component 12 further provides a connection pipe 17 for connection to the reservoir not shown. The component 13 also provides a connection pipe 18 for connection to the vacuum source 9, also not shown.

Figure 4 shows a partially sliced device for loading a three-dimensional body 1

containing the components shown in figure 3 in an assembled status. Further in figure 4 the three-dimensional body 1 which is of straight cylindrical shape is inserted inside the flow chamber enclosed by the mated recesses 14 inside the components 10 and 11. By applying a low vacuum of about 50 mbar at the left hand side of the flow chamber, i.e. by connecting a vacuum source to the connection pipe 18 the fluid which is a hydrogel, preferably an alginate sol, enters the flow chamber from the right to the left and penetrates the porous framework network of the β -TCP-three-dimensional body 1.

The cylindrical shaped three-dimensional body 1 is radially surrounded by a silicon seal 19 which ensures that the loading can take place only through the end surfaces of the micro-porous ceramic cylinder. In addition the silicon seal 19 further ensures that the ceramic body 1 does not move during the loading process.

In a not shown further preferred embodiment the components 10 and 11 can provide a recess into which a modular insert can be inserted which is individually adapted to the size and shape of the three-dimensional body to be loaded with the fluid. In the same way as in case of figure 3 the inner walls of the insert which contacts the three-dimensional body provides a silicon wall to ensure a gas/fluid tight enclosure of the lateral boundary layer of the respective three-dimensional body.

Already realized attempts show that it is possible to load a porous framework structure of a three-dimensional body with an alginate sol containing antibiotics and/or growths factors under ambient temperature conditions within a time duration of less than 15 minutes. The composition of the alginate sol can be varied in regard of viscosity and self curing properties which influence the time delivery of the bioactive agents contained within the alginate sol stored in the pore volume of the three-dimensional body after implanting into a patient.

List of References Numerous

1	three-dimensional body
2	first frontal boundary surface
3	second frontal boundary surface
4	lateral boundary surface
5	inner wall of the casing
6	casing
7	reservoir
8	fluid, hydrogel
9	vacuum source
10-13	components
14	recess
15	screw holes
16	O-Ring
17, 18	connection pipe
19	silicon seal

Claims

1. Method for loading a porous framework structure including a bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores with a fluid containing at least one bioactive component by using a pressure driven force for penetrating said fluid into said porous framework structure, comprising the following steps:
 - preparing or providing a three-dimensional body consisting at least partially of said porous framework structure having along one spatial direction two opposing frontal boundary surfaces, a first and second frontal boundary surface, being apart from each other and both of which adjoin at least one lateral boundary surface encircling said three-dimensional body,
 - sealing air tightly said at least one lateral boundary surface,
 - adjoining air tightly a reservoir of said fluid at the first frontal boundary surface and
 - applying a pressure difference between the first frontal boundary surface and the second frontal boundary surface such that the fluid penetrates through the porous framework structure along the spatial direction by pressure driven force only until the fluid exits over the entire second frontal boundary surface.
2. The method according to claim 1,
wherein the step of preparing or providing of the three-dimensional body is such that
 - a) the first and second frontal boundary surfaces are of same size and shape and overlap each other completely in projection of the spatial direction, or
 - b) the second frontal boundary surface is smaller or greater than the first frontal boundary surface and the second frontal boundary surface overlaps with the first frontal boundary surface completely in projection of the spatial direction.
3. The method according to claim 1 or 2,
wherein the three-dimensional body is of an straight cylindrical, wedge-shaped, cubic, prismatic or truncated conical shape.

4. The method according to one of the claims 1 to 3, wherein the porous framework structure made of biodegradable ceramic material contains pores having a mean pore diameter ranging between 1 μm to 10 μm , preferably 2 μm to 5 μm , the porous framework structure provides a porosity ranging between 30 % and 50%, preferably 40 % and the first and second frontal boundary surface are separated along the spatial direction by a distance ranging between 10 mm and 100 mm, preferably between 20 and 50 mm.

5. The method according to one of the claims 1 to 4, wherein the fluid provides a dynamical viscosity η [$\text{mPa} \cdot \text{s}$] ranging between 1,5 and 10^5 , preferably between 10^2 and $2 \cdot 10^4$, and a pressure difference between the first and second frontal boundary surface measures between 800 mbar and 1500 mbar, preferably 1000 mbar $\pm$ 100 mbar.

6. The method according to one of the claims 1 to 5, wherein applying the pressure difference is realized by applying an underpressure at the second frontal boundary surface and prevailing ambient pressure conditions in the fluid reservoir and said penetration of the fluid through the porous framework structure takes place under room temperature conditions, i.e. at temperatures between 15°C and 30 °C.

7. The method according to one of the claims 1 to 6, wherein said sealing of the at least one lateral boundary surface is performed by placing the three-dimensional body into a casing which contacts the at least one lateral boundary surface loose but airtight, while the casing allows free access to the first and second frontal boundary surface for connecting a vacuum source at the second frontal boundary surface and the fluid reservoir at the first frontal boundary surface of said three-dimensional body.

8. The method according to one of the claims 4 to 7, wherein the biodegradable ceramic material is a β -tricalcium phosphate (β -TCP), the fluid is an alginate sol and the at least one bioactive component is a antibiotics or growth factors.
9. The method according to claim 8, wherein the alginate sol bases on sodium alginate mixed in distilled water.
10. A three-dimensional body consisting at least partially of a porous framework structure including a bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores loaded with a fluid containing at least one bioactive component, wherein said porous framework structure encloses a pore volume which is completely filled with said fluid, and the at least one bioactive component has a heat resistance of less than 100°C, preferably less than 70°C.
11. The three dimensional body according to claim 10, wherein the fluid is a hydrogel, preferable an alginate sol, having self-curing properties and the at least one bioactive component is an antibiotics or growth factors.
12. The three dimensional body according to claims 10 or 11, wherein the three-dimensional body is of an straight cylindrical, wedge-shaped, cubic, prismatic or truncated conical shape and has along one spatial direction two opposing frontal boundary surfaces, a first and second frontal boundary surface, the porous framework structure made of biodegradable ceramic material contains pores having a mean pore diameter ranging between 1 μm to 10 μm , preferably 2 μm to 5 μm , the porous framework structure provides a porosity ranging between 30 % and 50%, preferably 40 % and

the first and second frontal boundary surface are separated along the spatial direction by a distance ranging between 10 mm and 100 mm, preferably between 20 and 50 mm.

13. The three dimensional body according to one of the claims 10 to 12 is made using the method according to one of the claims 1 to 9.

14. Device for loading a three dimensional body made of a porous framework structure including a bicontinuous morphology in at least partial areas or having non-interconnected side-by-side pores with a fluid containing at least one bioactive component

wherein a casing is provided into which said three dimensional body is insertable such that a contact wall of said casing or a contact wall of an insert into the casing encloses at least a lateral boundary surface of said three dimensional body airtightly but loose and

said casing provides along one spatial direction two opposing openings, a first and a second opening, the first opening is connected airtightly with a reservoir containing said fluid, and said second opening is connected airtightly with a vacuum source.

15. Device according to claim 14,
wherein said contact wall is made of silicone.

16. Device according to claim 14 or 15,
wherein the insert is adapted in size and shape to the three dimensional body and is insertable into the casing modularly.

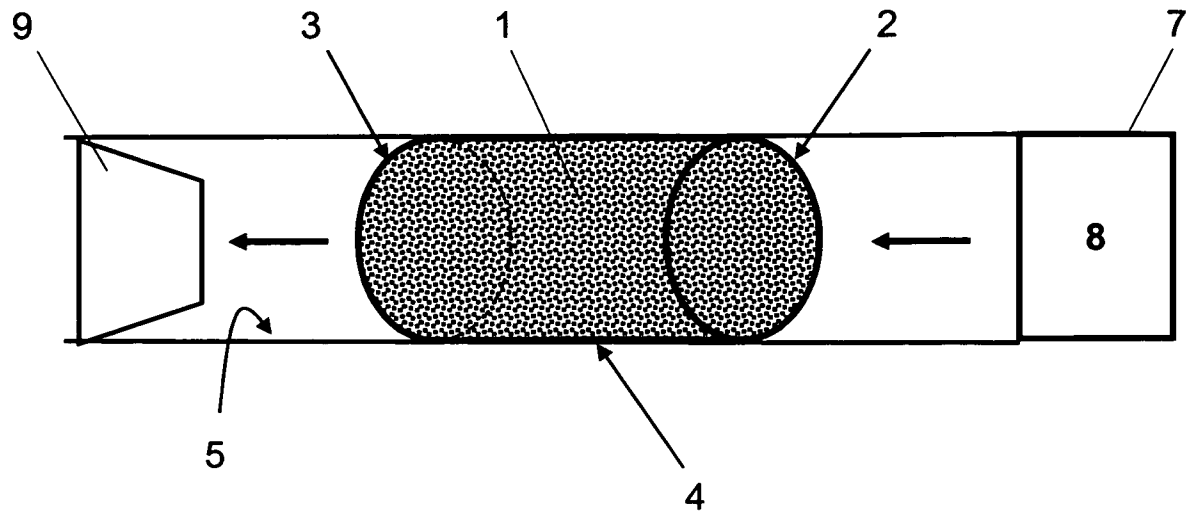


Fig. 1

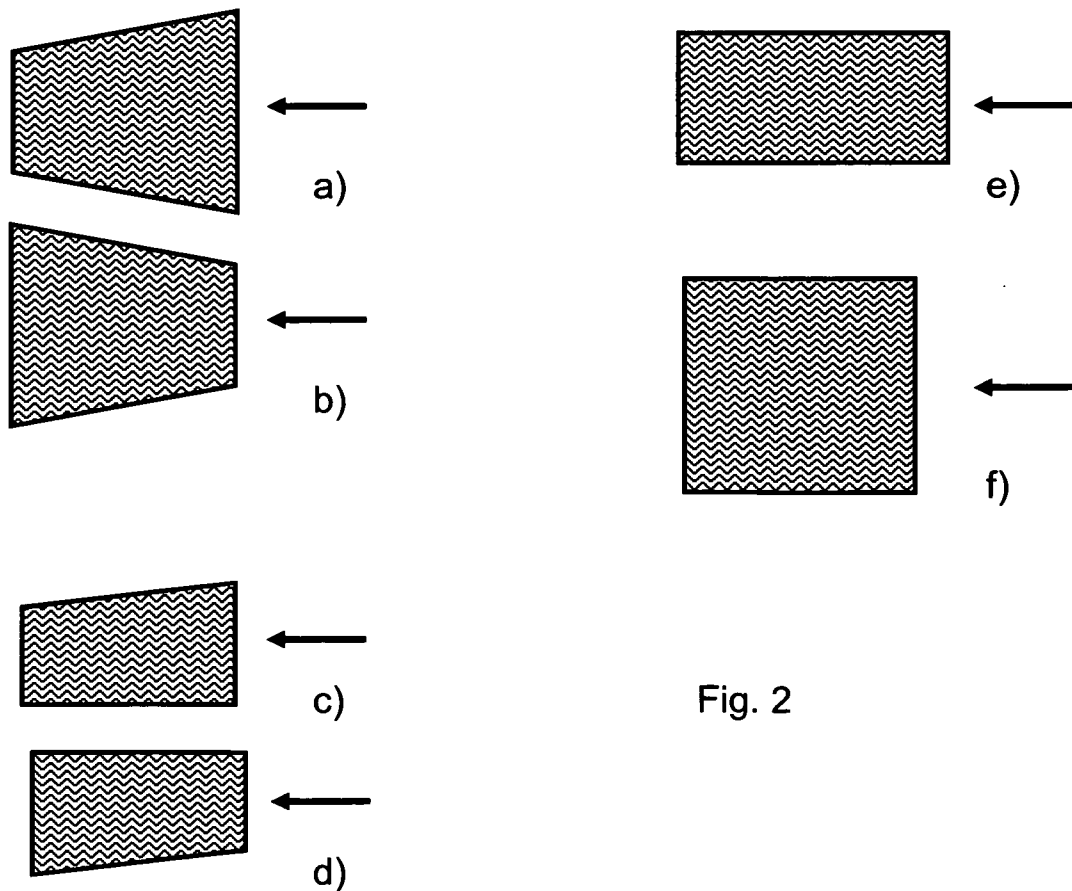


Fig. 2

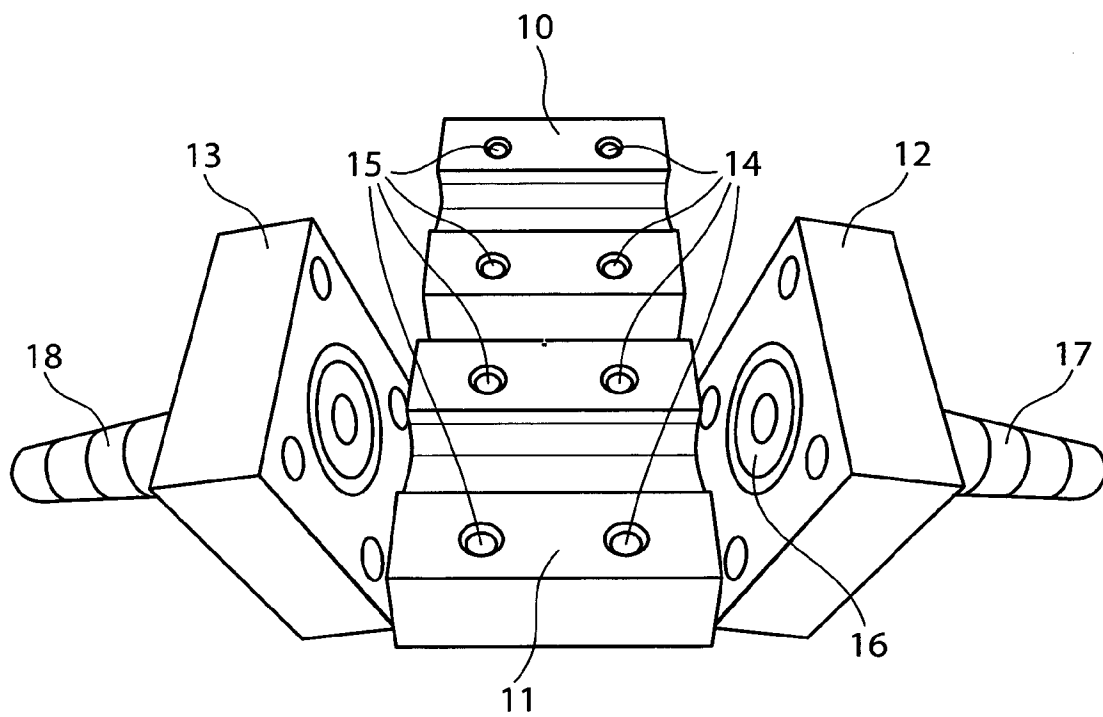


Fig. 3

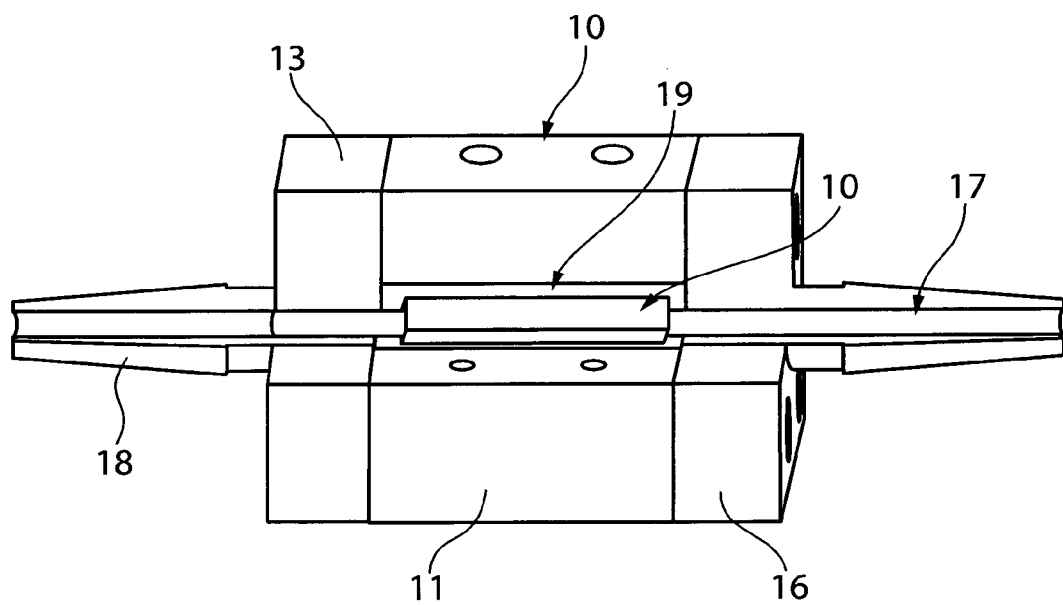


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/001935

A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/185299 A1 (NIES BERTHOLD [DE]) 22 July 2010 (2010-07-22)	1-3,5,7, 10,13, 14,16 4,8,9,12
Y	paragraph [0001] paragraph [0019] paragraph [0043] example 1 ----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

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International application No
PCT/EP2014/001935

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STEPHEN J. FLORCZYK ET AL: "Enhanced bone tissue formation by alginate gel-assisted cell seeding in porous ceramic scaffolds and sustained release of growth factor", JOURNAL OF BIOMEDICAL MATERIALS RESEARCH PART A, vol. 100A, no. 12, 6 July 2012 (2012-07-06), pages 3408-3415, XP055176143, ISSN: 1549-3296, DOI: 10.1002/jbm.a.34288 page 3409, left-hand column, line 40 - right-hand column, line 29 -----	4,8,9,12
X	US 2006/135938 A1 (MCKAY WILLIAM F [US]) 22 June 2006 (2006-06-22) paragraph [0021] paragraph [0026] - paragraph [0027] paragraph [0030] paragraph [0008] paragraph [0032] - paragraph [0035] figure 7 -----	1,2, 4-10,13
A	US 5 769 897 A (HAERLE ANTON [DE]) 23 June 1998 (1998-06-23) column 6, lines 12-32 column 9, line 49 - column 10, line 2 -----	1-10, 12-14,16

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
2-9, 12, 13, 16(completely); 1, 10, 14(partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2-5, 7-9, 12, 13, 16(completely); 1, 10, 14(partially)

Method for loading a three-dimensional body consisting of a porous framework structure and having two opposing frontal boundary surfaces, with a fluid containing a bioactive component by using a pressure driven force, wherein the porous framework is made of a biodegradable ceramic material with defined porosity; loaded three-dimensional body

2. claims: 6(completely); 1(partially)

Method for loading a three-dimensional body consisting of a porous framework structure and having two opposing frontal boundary surfaces, with a fluid containing a bioactive component by using a pressure driven force, wherein an underpressure is applied at the second frontal boundary surface of the three-dimensional body

3. claims: 11(completely); 10(partially)

Three-dimensional body with a porous framework structure, with pores loaded with a fluid containing a bioactive component, wherein the fluid is a hydrogel having self-curing properties

4. claims: 15(completely); 14(partially)

Device having a casing which provides along one spatial direction two opposing openings, and which is suitable for loading a three dimensional body of a porous framework with a fluid, wherein the contact wall of the casing is made of silicone

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/001935

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 2010185299	A1	22-07-2010	DE 112007003309 A5	29-10-2009
			EP 2111191 A2	28-10-2009
			JP 2010510817 A	08-04-2010
			US 2010185299 A1	22-07-2010
			WO 2008064672 A2	05-06-2008

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			WO 2006066125 A2	22-06-2006

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